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Circulating Cerebral S100B Protein Is Associated with Depressive Symptoms following Myocardial Infarction

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Key Words
S100B protein · Depressive symptoms · Myocardial infarction

Abstract
Background: Prevalence of depressive symptoms in the post-myocardial infarction (MI) period varies from 8 to 30%. Cerebral damage after MI, caused by transient ischemia, an inflammatory response or both, may contribute to development of post-MI depression. S100B is an established protein marker of cerebral damage. In a pilot study, the authors assessed whether S100B serum levels are: (1) increased during the week after MI, and (2) related to depressive symptoms during index hospital admission and the year following MI. ***Methods:*** This pilot study is a substudy of the Myocardial Infarction and Depression Intervention Trial (MIND-IT). In 48 patients, serum levels of S100B were available at 1, 2, 3, 4 and 8 days following MI. Subsequently, in 27 patients, depressive symptoms were measured at 0, 3, 6, 9 and 12 months following MI with the Beck Depression Inventory (BDI). In 21 of the initial 48 patients, BDI data were lacking due to refusals to fill out BDI forms or missing data. ***Results:*** Significant and transient increases in serum S100B were observed in 81.3% of the 48 patients: 37.5% reached S100B serum levels comparable to serum levels found in acute brain injury (>0.20 μg/l) and 43.8% reached mildly elevated S100B serum levels comparable to serum levels found in depressive disorder (0.10–0.20 μg/l). In 18.7%, no S100B was detected in serum. Using nonparametric Spearman rank correlation tests, a trend towards an association was found between serum S100B and depressive symptoms during the post-MI year (ρ values between 0.16 and 0.53) in 27 patients who completed both the S100B serum study and the BDI study. ***Conclusion:*** Transiently elevated levels of S100B are suggestive of minor acute cerebral damage in the first days following MI and associated with depressive symptoms in the year following MI. Cerebral damage could be an important mechanism in the pathogenesis in a subtype of post-MI depression.

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Introduction

Depressive symptoms following myocardial infarction (MI) have been associated with arrhythmic events and an increased risk of cardiac death up to 5 years after MI [1]. In a recent meta-analysis, the odds ratios for all-cause mortality and cardiac mortality were estimated to be 2.38 and 2.59, respectively [2]. The prevalence of depressive symptoms varies from 8 to 30% depending on the assessment method [3].

Cerebral damage, caused by transient ischemia, an inflammatory response or both, may contribute to induction of post-MI depression. Proinflammatory cytokines, including TNF-α, affect blood-brain barrier (BBB) integrity [4], and in experimental animal studies MI was associated with brain damage, most likely through immune-mediated processes [5]. Brain damage might also occur in human MI patients as a result of regular TNF-α release after MI [6]. Neuroimaging supports the association between subtle cerebral damage and depressive symptoms, since in clinically depressed but physically healthy patients cerebral white matter lesions (WML) are found [7]. WML in the elderly are associated with a 3- to 6-times higher risk of depressive symptoms compared to patients without WML [8]. Moreover, it was shown that MI and WML are related to each other [9].

Certain proteins in blood circulation may serve as markers of central nervous system (CNS) injury. Such an established marker is S100B, a calcium-binding protein of the S100 family that comprises 21 members. It is present in high concentrations in astroglial and oligodendroglial cells in the CNS, and is normally not detected in peripheral blood. Increased serum S100B levels may indicate glial alterations, either due to brain damage or functional secretion of S100B by astrocytes. Disruption of the BBB is mandatory to allow for cerebral efflux [10]. Extracellular S100B exerts a dual effect on neurons depending on its concentration, i.e. a pro-survival effect on neurons and stimulation of neurite outgrowth at nanomolar doses and a toxic effect at micromolar doses [11, 12]. Circulating S100B has a biological half-life of 25 min [13]. Following acute structural cerebral damage, S100B leaks into the bloodstream either directly from damaged tissue or indirectly via extra-cellular space. S100B efflux due to acute significant cerebral damage leads to a characteristic curve of S100B serum levels. Usually, the highest serum levels of S100B are observed 2–4 days after acute brain damage and normalize thereafter within 1–3 weeks [14]. S100B serum levels reflect S100B Cerebro Spinal Fluid levels [15]. After acute cerebral injury, serum S100B levels >0.30 μg/l at 48 h have predictive value for long-term anxiety [16], serum S100B >0.50 μg/l for persisting neuronal damage [17] and serum S100B >0.70 μg/l for death [18]. In several (neuro) psychiatric disorders, e.g. melancholic depression, elevation of S100B in serum is rather subtle (0.10–0.20 μg/l) and over time becomes more pronounced [12, 19–21].

S100B can also be found in serum after exercise with high cardiac output when activities included repetitive jarring movements or contact with the head (running), but not after exercise on a stationary bicycle, probably reflecting astroglial and/or BBB reaction in the first group [10].

However, in certain circumstances S100B is released from extra-cerebral tissues, e.g. after trauma, melanoma and cardiac surgery [22–24]. Therefore, it could be argued that serum S100B is not solely a marker for cerebral damage, but also a marker of cardiac damage. Fortunately, due to the short half-life of S100B and human renal clearance of 2 h, release of S100B from different damaged tissues leads to different time curves of the (peak) appearance of S100B in serum [14, 25]. This makes it possible to discriminate between different tissue origins of S100B, as was done in studies on cardiac surgery with cardiopulmonary bypass procedure (CPB) where both cerebral and cardiac sources of serum S100B were established [25]. During CPB, S100B was found in special reservoirs for cardiac surgical wound blood not contaminated by cerebral blood flow [26] and S100B serum levels measured immediately after cardiac surgery did correlate with measures of cardiac injury and not with neuropsychological outcome, which points to a cardiac source of S100B [27]. However, several other studies found a strong positive correlation between increased S100B serum levels and cerebral dysfunction after cardiac surgery, pointing to a cerebral origin of S100B in CPB [28–30]. The combination of these results suggested that in CPB two different pathophysiological mechanisms are responsible for S100B release in serum. Therefore, later on, the clinical significance of early and late release of S100B after CPB were analyzed separately [28]. Timing of its appearance in the circulation indicated that serum S100B has an early peak (immediately at the end of surgery) associated with cardiac damage measured by creatine kinase (CK) [27] or troponin I [25], and a late peak (5–48 h after surgery) associated with neurological dysfunction after cardiac surgery [25, 28]. As far as we know, data on the relation between S100B and MI are lacking.

To validate the hypothesis that cerebral damage may occur after MI and may contribute to induction of post-MI depression we investigated: (1) whether S100B serum

levels are increased during the week after MI, (2) the timing of its appearance in serum to discriminate between cardiac and cerebral sources, and (3) whether S100B serum levels in the first week after MI are related to depressive symptoms during hospital admission and the year following MI.

Methods

Study Population

Data were derived from the Myocardial Infarction and Depression Intervention Trial (MIND-IT), a multi-center randomized controlled study on the effects of antidepressant therapy for post-MI depression on cardiovascular prognosis. Inclusion and exclusion criteria have been described previously [31]. In brief, we recruited consecutive patients (September 1999–November 2002) hospitalized for acute MI in 10 hospitals across the Netherlands. Patients were enrolled if they met WHO MONICA criteria for definite MI. The patients for the S100B sub-study were all inpatients at the Coronary Care Unit of Medical Centre, Leeuwarden, the Netherlands, 1 of the 10 participating hospitals of the MIND-IT study. Exclusion criteria were: occurrence of MI while the patient was hospitalized for another reason, inability to participate in study procedures, a disease likely to influence short-term survival, receiving psychiatric treatment for depression already and participation in another clinical trial.

Procedures

Fifty-three consecutive patients (35 men and 18 women; age range 47–76 years) entered the S100B study. After written informed consent for participation in the S100B study, blood was collected by means of a venous puncture 5 times during the week after MI. Blood samples (6 ml) for S100B assays were taken on the day of admittance as soon as diagnosis of MI was given, before the start of thrombolytic therapy. Time interval between time of admittance for MI and the first S100B measurement varied between 1 and 3 h (mean 1.8 h). According to changes in the electrocardiograph, reperfusion was obtained 2–12 h after admittance for MI (mean 5 h). Information was obtained from clinical records by the participating cardiologist. Subsequently, on days 2, 3, 4 and 8, a fixed schedule was used and all venous punctures were performed at 8 a.m.

After blood for S100B determination was collected, patients were asked to participate in the MIND-IT study. As part of this study, patients with MI were screened for depressive symptoms during initial hospitalization (0 months) and 3, 6, 9 and 12 months after MI with the 21-item Beck Depression Inventory (BDI) questionnaire, an established method for screening depressive disorders in cardiac patients [32]. Demographic and medical information were obtained from the patients' medical records (table 1). From the 53 patients participating in the S100B study, 30 agreed to continue in the MIND-IT study and fill in BDI forms, whereas 23 refused. After BDI forms were completed, missing data were calculated for S100B only (n = 3), BDI only (n = 1) and both S100B and BDI (n = 2). Finally, complete data on S100B were available for 48 patients. Additionally, for 27 of these 48 patients, complete BDI data were available (fig. 1).

Table 1. Baseline and treatment characteristics for S100B

Variable	%
Male sex	58.3 (28)
Age >60 years	56.3 (27)
Anterior MI	33.3 (16)
Cardiac history (MI, PCI, CABG)	12.5 (6)
CK-MB (mean ± SD), U/l	197 ± 164
Peak CK (mean ± SD), U/l	2,080 ± 1,650
LVEF <45%	20.9 (10)
Medication at hospital admittance	
Acenocoumarol	2.1 (1)
β-Blockers	14.6 (7)
Diuretics	12.5 (6)
Calcium antagonists	8.3 (4)
Statins	12.5 (6)
ACE inhibitors	8.3 (4)
Medication during acute treatment phase	
Thrombolysis	100.0 (48)
Nitrates	100.0 (48)
Heparin	100.0 (48)
Ascal	100.0 (48)
Medication at day 8	
Nitrates	20.8 (10)
Ascal	83.3 (40)
Acenocoumarol	18.8 (9)
β-Blockers	85.4 (41)
Diuretics	22.9 (11)
Calcium antagonists	35.4 (17)
Statins	77.1 (37)
ACE inhibitors	27.1 (13)

Values are percentages with the numbers of subjects given in parentheses, unless otherwise indicated. PCI = Percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; ACE = angiotensin-converting enzyme.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the local ethical committees approved the design of the MIND-IT study. A separate informed consent was required by the local ethical committee of the Medical Centre of Leeuwarden for the collection of the S100B data. All participants were fully informed, and gave written informed consent.

Infarct Size

CK/CK-MB was used as a marker of the presence of MI, not for infarct size, as all patients received thrombolytic therapy after admission [33]. Left ventricular ejection fraction (LVEF) was used as a more reliable marker of infarct size. Details on the measurement of CK and LVEF were described previously [31, 34].

Biochemistry

Heparinized serum samples were centrifuged within 2 h at 2,300 *g*; aliquots were taken and frozen at –20°C until analysis.

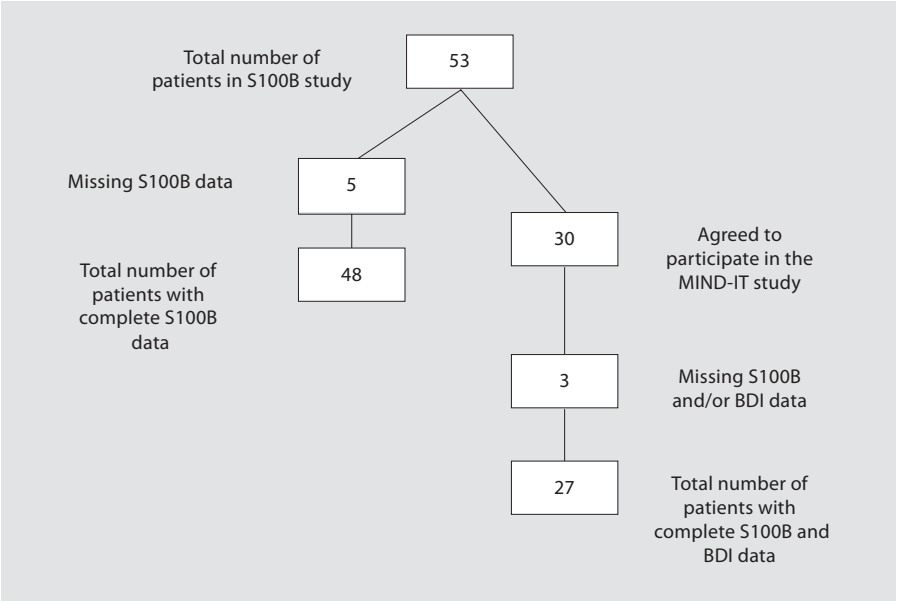

Fig. 1. Flow chart of patients in the S100B and subsequently the MIND-IT study. Missing data: S100B only (n = 3), BDI only (n = 1) and both S100B and BDI (n = 2).

S100B was determined with an immunofluorometric sandwich assay using a monoclonal anti-S100B chain antibody (LIA-mat R Sangtec Kit and Magic Little Analyzer 2, version 4.0; Sangtec, Bromma, Sweden). The Sangtec 100 LIA immunoluminometric assay uses tubes coated with 2 monoclonal antibodies as solid phase, and a monoclonal antibody for detection. The assay measures concentrations of S100B protein over the range of 0.02–20 μg/l. Measurements were performed according to the instructions of the manufacturer. Details about linearity, a description of the analytical technique, the accuracy and precision, and limit of quantification of the kit were described earlier [35].

The assay's threshold for detecting S100B is 0.02 μg/l. To minimize inter-assay variations, S100B was determined after all samples were collected.

Statistical Analysis

No sample size calculation was performed due to the exploratory nature of the trial. S100B data are expressed as medians and interquartile ranges, which are less affected by outliers in a small sample than means and standard deviations. Missing S100B data (6.7%) and missing data on the BDI (4.4%) were estimated by means of 2-way imputation [36]. The method was only used for patients with 2 or fewer missing values. As a consequence, 5 patients were excluded from further analyses on S100B, and 3 patients were excluded from analyses involving the BDI (fig. 1). Brain damage was expressed as both S100B peak value between days 2 and 4, and S100B area under the curve (AUC). AUC was calculated for each participant by integrating simple linear functions, which were set up using S100B at days 1, 2, 3, 4 and 8. The course of S100B during the first week after MI was evaluated with non-parametric pairwise comparisons between S100B at day 1, S100B peak value (days 2–4) and S100B at day 8 (Wilcoxon signed-rank test).

The relationships of S100B peak values and S100B AUC with BDI scores and LVEF, respectively, as a measures of MI severity, were evaluated with non-parametric Spearman rank correlation tests (ρ). Given the small sample size, α was set at 0.10 to increase statistical power.

With regard to the peak levels of serum S100B, 3 subcategories of patients were made in order to allow comparison (especially in the low range) with (neuro)psychiatric diseases in which elevated S100B concentrations are known to occur and are related to clinical symptoms. The first group was defined as having no S100B serum levels above 0.10 μg/l, which is comparable with healthy controls [37]. The second group was defined according to mildly elevated S100B levels between 0.10 and 0.20 μg/l, comparable with levels found in melancholic depression [21]. The third group was defined according to serum S100B levels >0.20 μg/l measured in various degrees of acute neurological pathology ranging from minor traumatic head injury [38] to stroke with unfavorable outcomes [10, 14, 17, 23, 28, 30, 38].

Results

Subjects (n = 30) who filled out a BDI did not differ from those who refused (n = 23) with respect to age, gender, co-morbidity, renal function, MI severity (LVEF) or S100B values.

Serum S100B Levels and Time Course

Non-parametric pairwise comparisons revealed significant differences for the sample as a whole between S100B at day 1 and S100B peak value ($Z = -4.01$; $p < 0.001$). No significant difference was found between S100B at day 1 and S100B at day 8 ($Z = -1.14$; $p = 0.25$). Figure 2 shows the temporal pattern of the median S100B levels and in-

terquartile range of the whole group (n = 48). Nine patients (18.7%) had no serum S100B levels above 0.10 μg/l. The second group of 21 patients (43.8%) had mildly elevated serum S100B levels between 0.10 and 0.20 μg/l, comparable with levels found in melancholic depression [21]. In the third group of 18 patients (37.5%), serum S100B levels were significantly elevated and reached levels >0.20 μg/l as measured in acute neurological pathology. Five of these reached values analogous to values seen in the range of severe cerebral pathology, e.g. stroke (>0.35 μg/l; fig. 3).

Serum S100B and Infarct Size

S100B peak value (ρ = –0.14; p = 0.49) and S100B AUC (ρ = 0.03; p = 0.90) were not associated with LVEF (n = 48).

Serum S100B and Depressive Symptoms

Depressive symptoms assessed at initial hospitalization were not related to serum S100B peak value and serum S100B AUC (fig. 3; n = 27). However, serum S100B peak values and serum S100B AUC were both associated with the BDI score of depressive symptoms at follow-up (fig. 3). As shown in table 2, a consistent pattern of significant correlations and trends was found for depressive symptoms assessed at 3, 6, 9 and 12 months after MI (n = 27).

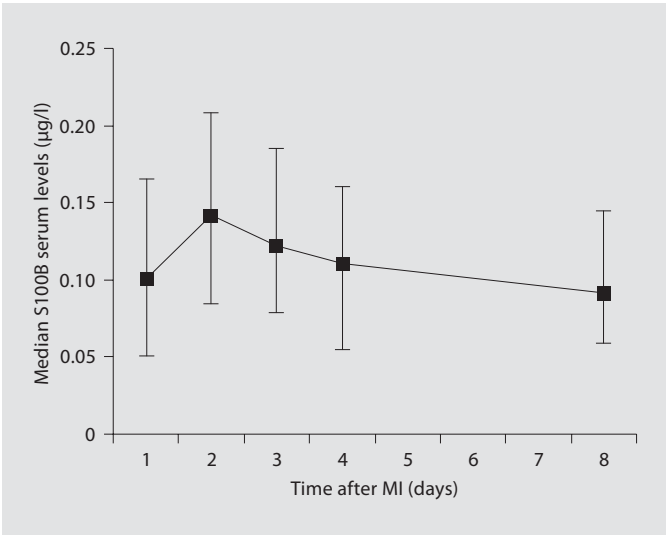

Fig. 2. Time course of median S100B serum levels of the whole sample following MI (n = 48). The error bars represent the interquartile range.

Table 2. Spearman's ρ correlation coefficients for S100B (peak value and AUC) and depressive symptoms at baseline and follow-up

Depressive symptoms	S100B peak value	S100B AUC
First week after MI	0.07	0.16
3-month follow-up	0.47**	0.34*
6-month follow-up	0.30	0.23
9-month follow-up	0.53***	0.34*
12-month follow-up	0.36*	0.16

* p < 0.10; ** p < 0.05; *** p < 0.01.

Discussion

This pilot study is the first to report that S100B serum levels may be increased in the first week after MI in a time and peak pattern comparable with serum S100B release after acute cerebral damage (fig. 2). Moreover, a trend towards an association was found between serum S100B levels and depressive symptoms during the first year after MI, especially at the later measurement points 3–12 months after MI (table 2). S100B serum levels were not associated with infarct size as derived from LVEF. These data indicate that cerebral damage may play a role in the development of post-MI depression.

Although we measured plasma CK/CK-MB, it was not used as a marker of infarct size as early thrombolytic therapy is a confounder in this situation [33]. Therefore, we preferred LVEF as a marker for infarct size.

The results are consistent with previous studies on the association between the late increase in S100B serum levels and cognitive/neurological dysfunction after CPB [25, 28]. In late release, defined as the first 5–48 h after CPB, S100B serum contamination from cardiac sources is presumed to be insignificant [24, 28]. Our study results are also in line with the observation that heightened S100B serum levels (>0.30 μg/l) 48 h after CPB might predict long-term (3–6 years) anxiety [16] demonstrating that a single cardiac event might result in long lasting psychiatric symptoms. In light of these studies it is not surprising that another single cardiac event as MI may result in long-lasting depressive symptoms.

As the relation between S100B serum levels and MI is unknown, the question to be considered here is whether the S100B serum levels after MI have a cerebral, cardiac or mixed origin. Several arguments favor a predominant-

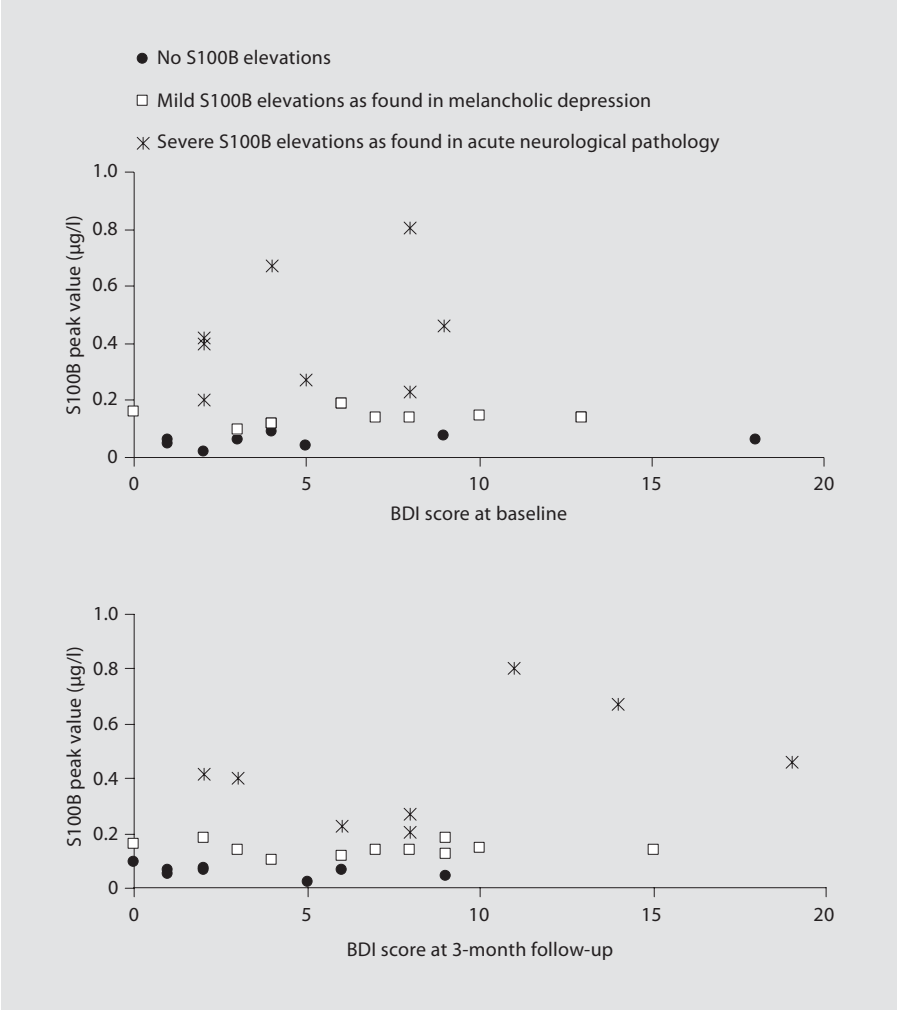

Fig. 3. Scatter plots: relation between serum S100B peak value (µg/l) and BDI score.

ly cerebral origin of the S100B serum levels we found in this pilot study. The isolated ischemic rat heart releases S100B, but only for a maximum of 60 min after myocardial ischemia [39]. As yet no data are available in man. Considering the short biological half-life of S100B of 25 min and human renal clearance of 2 h [13] the supposed early but transient cardiac release of S100B due to MI will probably only last from some minutes to an hour. This rise will probably remain unnoticed when examining serum samples taken at least several hours following MI, as was the case in this study. As the average time between hospital admittance for MI and the first serum S100B measurement point was 1.8 h, and time between admittance for MI and reperfusion 5 h, we cannot completely rule out that cardiac S100B added to the amount of serum S100B, especially in the serum S100B measurements on day 1. For the measurements of serum S100B on days 2–8 this is highly unlikely, considering the half-life of 25 min. Moreover, we did not find any association between LVEF and S100B serum levels, which also points to an extracardiac origin of S100B.

In addition, the cerebral origin of serum S100B is strongly backed up by the time course, with a peak of median S100B serum levels on days 2–3 after MI (fig. 2). The pattern is the same as seen after primary acute cerebral injury [14] and also corresponds with the time pattern of late-release serum S100B associated with cerebral damage after CPB [25, 28]. The observed S100B serum levels (fig. 3) are also comparable to S100B levels found in various neurological and psychiatric study populations.

In order to estimate the clinical significance of the measured S100B serum levels, we divided our study population into 3 subgroups. This made comparison possible with previous study populations in which a relation was

established between serum S100B and the clinical disease examined. The first group (18.7%) had no S100B elevation at all, therefore the conclusion that MI does not automatically lead to late (5–48 h) release of serum S100B is justified. The second group (43.8%) was defined according to S100B levels found in depressive disorder (0.10–0.20 μg/l) [21]. The third group (37.5%) had levels >0.20 μg/l that can be found in various forms of cerebral damage ranging from minor traumatic head injury to stroke [10, 14, 17, 23, 28, 30, 38]. This last comparison adds to the preliminary conclusion that the serum S100B levels we found might have clinical relevance.

The variation in S100B levels between the 3 groups is probably due to individual variation in cerebral vulnerability for changes after MI, which is consistent with the observation that patients with a previous history of stroke or transient ischemic attack had higher levels of S100B directly after CPB than those who did not [28]. We presume that the incidental high serum S100B levels >0.35 μg/l in the range of serious neurological damage [10, 30] may point to small non-progressive brain lesions, formed shortly before blood was collected as none of the patients experienced physical neurological symptoms. Consistent with the latter is that in a serum S100B serial measurement study of head trauma, values of 0.9 μg/l were measured with a rapid decline to 0.2–0.4 μg/l during the first 12 h after the trauma [40]. None of the patients in our study had persistently high serum S100B values.

The clinical relevance of glial protein S100B in depressive disorder has not yet been established. Histopathological postmortem studies showed consistent reductions in glial cell density in prefrontal brain regions of depressive patients [41]. A relation between elevated serum S100B levels and melancholic major depression (a subtype of depressive disorder) was established in physically healthy patients [19]. It was replicated for other but not all types of depressive disorder [19, 21]. In case of association between depressive disorder and S100B serum levels, the levels were consistently between 0.05 and 0.2 μg/l [21].

Antidepressant drugs influence secretion of S100B by astrocytes via the serotonergic system [42]. S100B may induce neurogenesis [43] that is required for behavioral effects of antidepressants [44]. Four treatment studies showed that S100B decreases after successful antidepressant treatment [20, 21, 45, 46]. Patients with increased S100B levels had a better therapeutic response than those with normal S100B levels [46]. However, the effect sizes differ [21], and this may have its origin in the fact that depressive disorder is a heterogeneous group of psychiatric disorders with different neurobiological and psychological characteristics. It is a spectrum disorder with at one end characteristic predominant psychological symptoms, possibly reflecting only a 'psychological' reaction to stressful circumstances including a life-threatening disease; the other end is characterized by severe somatic symptoms combined with a typical cognitive profile, and related to somatic diseases such as brain damage, MI and severe LV dysfunction in which it is difficult to assess whether the depression is a 'biological' consequence of the illness itself or not [8, 47].

The MIND-IT study provided evidence for the same heterogeneity in post-MI depression [47]. Moreover, it was found that a significant number of patients were depressed before MI, and impaired cardiovascular prognosis and heightened mortality were found only in patients with incident post-MI depression. Incident post-MI depression might be a depressive subtype that is a pathophysiological consequence of cardiovascular illness itself [48].

The association of elevated S100B levels in the first week after MI with depressive symptoms at 3- to 12-month follow-up indicates that de novo cerebral damage may contribute to the development of post-MI depression. This is also indicative of a specific (biological) subtype of post-MI depression, and in line with earlier reports on cardiac events and induction of psychopathology [16]. Although there seems to be a connection, the small number of patients causes a statistical weakness of association between S100B and depressive symptoms. Large-scale studies are necessary to gather more in-depth insight into the connection between S100B levels and depressive symptoms.

As different subtypes of post-MI depression have a different response to treatment and non-response is associated with more cardiac events [48], it is important to obtain knowledge about possible mechanisms in the association between depressive symptoms and MI in the several subtypes of post-MI depression in order to develop prophylactic and therapeutic regimens, both in terms of quality of life and prognosis.

Given the dual (survival and toxic) effect on neurons and its wide variety of intra- and extra-cellular functions, it remains to be proven if the increase in S100B serum concentration in our study is due to substantial destruction of CNS tissue or to an active release of S100B from intact astrocytes attempting to repair neuronal damage.

The present findings need to be interpreted with caution, given the small number of subjects, the absence of neuropsychological tests to assess cognitive impairment and the lack of inflammatory data. Nor do we exclude the

possibility that brain damage was caused by complications of thrombolytic therapy [49]. Nonetheless, the results do warrant further research to discern the interrelation of post-MI depression, MI-related brain damage, inflammation and coronary heart disease.

In conclusion, our data are the first to show a release of S100B in serum during the first week after MI, and a positive correlation between serum S100B and depressive symptoms at 3- to 12-month follow-up. Although we do not entirely rule out the influence of cardiac S100B, several arguments favor cerebral damage as the main source of the serum-derived S100B. The arguments include the positive correlation between S100B and depressive symptoms at 3- to 12-month follow-up, the time course of the curve of S100B in the first week after MI and the absence of S100B elevation in 18% of the patients during the initial hospitalization for MI. The present data may imply that post-MI cerebral damage is associated with a subtype of post-MI depression.

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Clinical Centers: Flevo Hospital, Almere: A.S.J.M. Sadee MD, L.M. Konijnenberg MD. Academic Medical Center, Amsterdam: G. Casteelen MD, A.M.G. Kuyper MD, R.J.G. Peters MD, PhD. Slotervaart Hospital, Amsterdam: M. Bax MD. Nij Smellinghe Hospital, Drachten: M. van der Linde MD, PhD, H. Teunenbroek MD. Medical Spectrum Twente, Enschede: D.G. Buiten MD, G.P. Molhoek MD, PhD. University Hospital Groningen: J.A. den Boer MD, PhD, J.F. May MD, PhD. Tjongerschans Hospital, Heerenveen: H.P. den Daas MD, D.G. Jochemsen MD. Atrium Medical Center, Heerlen: L.H.B. Baur MD, PhD, C.J.M. van den Berg MD, PhD. Medical Center Leeuwarden: D.M. Tulner MD, C.J. de Vries MD. University Hospital Maastricht: A. Honig MD, PhD, P.M.J.C. Kuijpers MD, A. Schins MD, PhD. *Endpoint Committee:* P.M.J.C. Kuijpers MD, PhD, J.F. May MD, PhD, R.J.G. Peters MD, PhD.

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